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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,434	02/24/2006	Tzung-Horng Yang	037003-0313985	7954

27499 7590 06/26/2008

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
06/26/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket_ip@pillsburylaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/518,434	YANG ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,22-82 and 102* is/are pending in the application.

4a) Of the above claim(s) *1,82 and 102* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-81* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/20/04; 5/2/05; 7/17/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendment filed 20 December 2004.

Election/Restrictions

2. Applicant's election without traverse of the invention of Group VI, claims 22-81 in the reply filed on 16 April 2008 is acknowledged.

3. Claims 1, 82 and 102 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 22-81 are under consideration to the extent that the antibody is an anti-CD20 antibody or rituximab.

Information Disclosure Statement

5. The information disclosure statement (IDS) submitted on 20 December 2004, 02 May 2005 and 17 July 2006 have been fully considered by the examiner. A signed and initialed copy of each IDS is included with the instant Office Action. It is noted that reference AR on the IDS filed 7/17/2006 is a duplicate citation of reference 3 on the IDS filed 12/20//04. Accordingly, reference AR has been crossed out on the IDS filed 7/17/06 to avoid delays at the time of issue.

Specification

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the method for producing a concentrated anti-CD20 antibody preparation.

Appropriate correction is required.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 22-32, 34-40, 42-52, 54-60, 62-72 and 74-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al (U.S. Patent 6,171,586 B1, 6/13/1997, IDS reference 3 filed 12/20/2004) in view of Relton et al (US Patent 6,252,055, 11/12/1998, IDS reference BR filed 5/2/2005).

Lam et al teach the preparation of anti-CD20 antibody compositions, including pharmaceutical compositions comprising an anti-CD20 monoclonal, chimeric or humanized antibody in 5 mM to 30 mM, or 10 mM acetate (e.g., sodium acetate) or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0, which solves the need in the art for a stable aqueous pharmaceutical formulation comprising an anti-CD20 antibody suitable for therapeutic use in treating B cell lymphoma patients (see entire document, particularly cols. 2, 5-10, 13-14, 22-2, Example 2 and claims). Lam et al do not specifically teach subjecting the antibody compositions to membrane filtration to produce an antibody composition having a higher concentration of antibodies than the initial antibody preparation, wherein the concentration of the antibodies is at least 50 mg/ml, or at least 100 mg/ml, or wherein the antibodies of the antibody composition have one or more of the isotypes selected from IgG, IgG_1, IgG_4, IgM, IgA, IgD and IgE. These deficiencies are made up for in the teachings of Relton et al.

Relton et al teach methods for producing concentrated antibody preparations and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, wherein the antibody is a monoclonal, chimeric or humanized antibody and has an isotype selected from IgG_1, IgG_2, IgG_3, IgG_4, IgM, IgA, IgD and IgE and the antibody is specific for a tumor cell marker for human tumor therapy, wherein the method comprises providing an antibody preparation, filtering the antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and leading to the successful concentration of antibody at a concentration of 100 mg/ml or greater, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody (see entire document, particularly cols. 1-2, 3, lines 18-27, 35-37, col. 5 and claims).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for

producing a concentrated anti-CD20 antibody preparation (e.g., monoclonal, chimeric and humanized anti-CD20 antibodies and having and having an IgG_1, IgG_2, IgG_3, IgG_4, IgM, IgA, IgD or IgE isotype) and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an anti-CD20 antibody preparation comprising anti-CD20 antibodies in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of anti-CD20 antibodies at a concentration of 100 mg/ml or greater for therapeutic benefit in human B cell lymphoma patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a concentrated anti-CD20 antibody preparation (e.g., monoclonal, chimeric and humanized anti-CD20 antibodies and having an IgG_1, IgG_2, IgG_3, IgG_4, IgM, IgA, IgD or IgE isotype) and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an anti-CD20 antibody preparation comprising anti-CD20 antibodies in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of anti-CD20 antibodies at a concentration of 100 mg/ml or greater for therapeutic benefit in human B cell lymphoma patients in view of Lam et and Relton et al because Lam et al teach the preparation of anti-CD20 antibody compositions, including pharmaceutical compositions comprising an anti-CD20 monoclonal, chimeric or humanized antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0, which solves the need in the art for

a stable aqueous pharmaceutical formulation comprising an anti-CD20 antibody suitable for therapeutic use in treating B cell lymphoma patients and Relton et al teach methods for producing concentrated antibody preparations and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an antibody preparation, filtering the antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and leading to the successful concentration of antibody at a concentration of 100 mg/ml or greater, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody and wherein the antibody is a monoclonal, chimeric or humanized antibody and has an isotype selected from IgG_1, IgG_2, IgG_3, IgG_4, IgM, IgA, IgD and IgE and the antibody is specific for a tumor cell marker for human tumor therapy. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to concentrate the anti-CD20 monoclonal, chimeric and humanized antibody preparations of Lam et al according to the method of Relton, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody and also solves the need in the art for a stable aqueous pharmaceutical formulation comprising an anti-CD20 antibody suitable for therapy in B cell lymphoma patients. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See also *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a method for making a concentrated anti-CD20 antibody preparation (e.g., monoclonal, chimeric and humanized anti-

CD20 antibodies and having an IgG_1, IgG_2, IgG_3, IgG_4, IgM, IgA, IgD or IgE isotype) and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an anti-CD20 antibody preparation comprising anti-CD20 antibodies in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of anti-CD20 antibodies at a concentration of 100 mg/ml or greater for therapeutic benefit in human lymphoma patients in view of Lam et and Relton et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claims 22, 41-42, 61-62 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al (U.S. Patent 6,171,586 B1, 6/13/1997, IDS reference 3 filed 12/20/2004) in view of Relton et al (US Patent 6,252,055, 11/12/1998, IDS reference BR filed 5/2/2005) and Maloney et al (Blood, 90(6):2188-2195, 1997).

Lam et al have been described supra. Lam et al do not specifically teach subjecting the antibody compositions to membrane filtration to produce an antibody composition having a higher concentration of antibodies than the initial antibody preparation or the chimeric anti-CD20 antibody, rituximab. These deficiencies are made up for in the teachings of Relton et al and Maloney et al.

Relton et al have been described supra.

Maloney et al teach the administration of IDEC-C2B8 chimeric anti-CD20 monoclonal antibody (also known as rituximab) in human non-Hodgkin's lymphoma patients that results in tumor inhibition and according to Maloney et al

presents the opportunity to obtain meaningful tumor reductions with minimal toxicity (see entire document, particularly pp. 2188, 2190-2191, 2194 and Fig. 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for producing a concentrated IDEC-C2B8 chimeric anti-CD20 antibody preparation and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an IDEC-C2B8 chimeric anti-CD20 antibody preparation comprising the IDEC-C2B8 chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the IDEC-C2B8 chimeric anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of the IDEC-C2B8 chimeric anti-CD20 antibody preparation at a concentration of 100 mg/ml or greater for therapeutic benefit in human non-Hodgkin's lymphoma patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a concentrated IDEC-C2B8 chimeric anti-CD20 antibody preparation and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an IDEC-C2B8 chimeric anti-CD20 antibody preparation comprising the IDEC-C2B8 chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the IDEC-C2B8 chimeric anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of the IDEC-C2B8 chimeric anti-CD20 antibody preparation at a concentration of 100 mg/ml or greater for therapeutic benefit in human non-Hodgkin's lymphoma patients in view of Lam et al and Relton et al

and Maloney et al because Lam et al teach the preparation of anti-CD20 antibody compositions, including pharmaceutical compositions comprising a chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0, which solves the need in the art for a stable aqueous pharmaceutical formulation comprising an anti-CD20 antibody suitable for therapeutic use in treating B cell lymphoma patients and Relton et al teach methods for producing concentrated antibody preparations and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an antibody preparation, filtering the antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and leading to the successful concentration of antibody at a concentration of 100 mg/ml or greater, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody and Maloney et al teach that the administration of IDEC-C2B8 chimeric anti-CD20 monoclonal antibody (also known as rituximab) in human non-Hodgkin's lymphoma patients results in tumor inhibition and the IDEC-C2B8 chimeric anti-CD20 monoclonal antibody presents the opportunity to obtain meaningful tumor reductions with minimal toxicity according to Maloney et al. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to produce an anti-CD20 antibody composition comprising the IDEC-C2B8 chimeric anti-CD20 monoclonal antibody of Maloney and concentrate the IDEC-C2B8 chimeric anti-CD20 antibody composition according to the method of Relton, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody and the IDEC-C2B8 chimeric anti-CD20 monoclonal antibody of Maloney is advantageous in that it reduces tumor burden in non-Hodgkin's lymphoma patients with minimal toxicity. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing

line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Semaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See also *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a method for producing a concentrated IDEC-C2B8 chimeric anti-CD20 antibody preparation and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an IDEC-C2B8 chimeric anti-CD20 antibody preparation comprising the IDEC-C2B8 chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the IDEC-C2B8 chimeric anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of the IDEC-C2B8 chimeric anti-CD20 antibody preparation at a concentration of 100 mg/ml or greater for therapeutic benefit in human non-Hodgkin's lymphoma patients in view of Lam et and Relton et al and Maloney et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

10. Claims 22, 31-33, 42, 51-53, 62 and 71-73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lam et al (U.S. Patent 6,171,586 B1, 6/13/1997, IDS reference 3 filed 12/20/2004) in view of Relton et al (US Patent 6,252,055, 11/12/1998, IDS reference BR filed 5/2/2005) and Newman et al (US Patent 5,658,570, issued 8/19/1997).

Lam et al have been described supra. Lam et al do not specifically teach subjecting the antibody compositions to membrane filtration to produce an antibody composition having a higher concentration of antibodies than the initial antibody preparation or that the chimeric anti-CD20 antibodies comprise the variable regions of Old World monkey and human constant regions. These deficiencies are made up for in the teachings of Relton et al and Newton et al.

Relton et al have been described supra.

Newman et al teach chimeric anti-CD20 antibodies comprising the variable regions of Old World monkeys and human constant regions wherein the antibodies are less immunogenic in humans compared to mouse monoclonal antibodies and hence, better suited for human therapy (see entire document, particularly cols. 1-3 and 6-9).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a method for producing a concentrated Old World monkey chimeric anti-CD20 antibody preparation and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an Old World monkey chimeric anti-CD20 antibody preparation comprising the Old World monkey chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the Old World monkey chimeric anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of the Old World monkey chimeric anti-CD20 antibody preparation at a concentration of 100 mg/ml or greater for therapeutic benefit in human B cell lymphoma patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a method for producing a concentrated Old World monkey chimeric anti-CD20 antibody preparation and

pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an Old World monkey chimeric anti-CD20 antibody preparation comprising the Old World monkey chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the Old World monkey chimeric anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of the Old World monkey chimeric anti-CD20 antibody preparation at a concentration of 100 mg/ml or greater for therapeutic benefit in human B cell lymphoma patients in view of Lam et al and Relton et al and Newman et al because Lam et al teach the preparation of anti-CD20 antibody compositions, including pharmaceutical compositions comprising a chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0, which solves the need in the art for a stable aqueous pharmaceutical formulation comprising an anti-CD20 antibody suitable for therapeutic use in treating B cell lymphoma patients and Relton et al teach methods for producing concentrated antibody preparations and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an antibody preparation, filtering the antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and leading to the successful concentration of antibody at a concentration of 100 mg/ml or greater, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody and Newman et al teach chimeric anti-CD20 antibodies comprising the variable regions of Old World monkey antibodies and human constant regions that are less immunogenic in humans compared to mouse monoclonal antibodies and hence, better suited for human therapy.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated by the goal of reducing antibody immunogenicity in human B cell lymphoma patients and produced an anti-CD20 antibody preparation comprising chimeric anti-CD20 monoclonal antibodies comprising the variable regions of Old World monkey antibodies and human constant regions in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and concentrate the Old World monkey chimeric anti-CD20 antibody preparation according to the method of Relton, which overcomes the art recognized problems of low recovery rates and precipitate formation when concentrating antibody. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983). See also *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007). Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a method for producing a concentrated Old World monkey chimeric anti-CD20 antibody preparation and pharmaceutical compositions comprising such and a physiologically acceptable carrier or diluent, comprising providing an Old World monkey chimeric anti-CD20 antibody preparation comprising the Old World monkey chimeric anti-CD20 antibody in 5 mM to 30 mM, or 10 mM acetate or histidine buffer in the pH range of 4.5 to 6.0, 4.8 to 5.5, or 5.0 and filtering the Old World monkey chimeric anti-CD20 antibody preparation through a retentate side of a filtering membrane using ultrafiltration to produce a filtrate and recirculating the filtrate back to said retentate side of the filtering membrane at a reduced circulation rate, thereby reducing sheer stresses and the successful concentration of the Old World monkey chimeric anti-CD20 antibody preparation at a concentration of 100 mg/ml or greater for therapeutic benefit in human B cell lymphoma patients in view of Lam et al and Relton et al and Newman et al.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832.

The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David J. Blanchard/
Primary Examiner, A.U. 1643